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Frank C. Eisenschenk

Frank C. Eisenschenk, Ph.D., Patent Attorney

REQUEST FOR CERTIFICATE OF
CORRECTION UNDER 37 CFR 1.322
and 1.323

Docket No. G-069US02CIP

Patent No. 6,977,145

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicants : Yves Fouillet, Claude Vauchier, Jean-Frederic Clerc, Christine Peponnet,
Patricia Claustre, Raymond Charles, and Nicolas Sarrut
Issued : December 20, 2005
Patent No. : 6,977,145
For : Method for Carrying Out a Biochemical Protocol in Continuous Flow in a
Microreactor

Mail Stop Certificate of Corrections Branch
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Certificate
MAR 08 2006
of Correction

REQUEST FOR CERTIFICATE OF CORRECTION
UNDER 37 CFR 1.322 (OFFICE MISTAKE) AND
UNDER 37 CFR 1.323 (APPLICANTS' MISTAKE)

Sir:

A Certificate of Correction (in duplicate) for the above-identified patent has been prepared and is attached hereto.

In the left-hand column below is the column and line number where errors occurred in the patent. In the right-hand column is the page and line number in the application where the correct information appears.

Patent Reads:

Title page, No. (75):

"Serono Genetics Institute S.A."

03/06/2006 YPOLITE1 00000128 190065 6977145

01 FC:1811

100.00 DA

Application Reads:

Recorded Assignment dated July 9, 2001,
Reel/Frame: 011943/0474:

--Serono Genetics Institute S.A. and
Commissariat a l'Energie Atomique--

MAR 8 2006

Column 7, line 62:
"along I-II"

Page 11, line 19:
--along II-II--

Column 25, line 25:
"Eallele-specific"

Page 39, line 22:
--allele-specific--

Column 42, line 6:
"Genotypin:"

Page 65, line 18:
--Genotyping:--

Column 62, line 27:
"whwrein"

Amendment dated October 5, 2004 (original
claim 9 renumbered as claim 1):
--wherein--

Column 63, line 34:
"such hat"

Amendment dated October 5, 2004 (original
claim 51 renumbered as claim 24):
--such that--

Patent Reads:

Application Should Read:

Column 64, line 8:
"member is"

Amendment dated October 5, 2004 (original
claim 59 renumbered as claim 32):
--member that is--

Patent Reads:

Application Reads:

Column 65, line 1
"method claim 47"

Amendment dated October 5, 2004 (original
claim 75 renumbered as claim 48):
--method of claim 47--

True and correct copies of pages 11, 39, and 65 of the specification as filed, the Amendment dated October 5, 2004, and the Notice of Recordation of Assignment Document dated July 9, 2001, which support Applicants' assertion of the errors on the part of the Patent Office, accompany this Certificate of Correction. In addition, attached is a copy of a decision on petition dated September 27, 2005 instructing the Certificates of Correction Branch to issue a certificate of correction which sets forth Serono Genetics Institute S.A. and Commissariat A L'Energie Atomique as the assignees.

The Commissioner is authorized to charge the fee of \$100.00 for the amendment to Deposit Account No. 19-0065. The Commissioner is also authorized to charge any additional

fees as required under 37 CFR 1.20(a) to Deposit Account No. 19-0065. Two copies of this letter are enclosed for Deposit Account authorization.

Approval of the Certificate of Correction is respectfully requested.

Respectfully submitted,



Frank C. Eisenschenk, Ph.D.
Patent Attorney
Registration No. 45,332
Phone No.: 352-375-8100
Fax No.: 352-372-5800
Address: P.O. Box 142950
Gainesville, FL 32614-2950

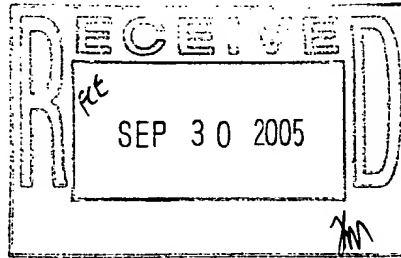
FCE/gyl

Attachments: Certificate of Correction (in duplicate)
Copies of pages 11, 39, and 65 of the specification
Copy of Amendment dated October 5, 2004
Copy of Notice of Recordation of Assignment Document dated July 9, 2001
Copy of decision on petition dated September 27, 2005
Two copies of this letter



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Saliwanchik, Lloyd & Saliwanchik
P. O. Box 142950
Gainesville, FL 32614-2950

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OFFICE OF PETITIONS

In re Application of	:	
Yves Fouillet, et al.	:	
Application No. 09/772,280	:	ON PETITION
Filed: January 29, 2001	:	
Attorney Docket No. G-069US02CIP	:	

This is a decision on the petition, filed July 15, 2005, which is being treated as a request under 37 CFR 3.81(b)¹ to add the second assignee's name on the Fee(s) Transmittal form PTOL-85(b) so that the Letters Patent will issue to both assignees.

The request is **DISMISSED**.

Petitioner states that the second assignee's name is Commissariat A L'Energie Atomique and was unintentionally not included on the Fee(s) Transmittal form PTOL-85(b) at the time of payment of the issue fee. Accordingly, petitioner requests that the patent issue to Serono Genetics Institute, S.A. and Commissariat A L'Energie Atomique.

37 CFR 3.81(b), effective June 25, 2004, reads:

After payment of the issue fee: Any request for issuance of an application in the name of the assignee submitted after the date of payment of the issue fee, and any request for a patent to be corrected to state the name of the assignee, must state that the assignment was submitted for recordation as set forth in § 3.11 before issuance of the patent, and must include a request for a certificate of correction under § 1.323 of this chapter (accompanied by the fee set forth in § 1.20(a) and the processing fee set forth in § 1.17(i) of this chapter.

¹ See Official Gazette of June 22, 2004

MAR 8 2006

The request under 37 CFR 3.81(b) was not accompanied by a request for a certificate of correction (and fee) as required by 3.81(b). As petitioner has failed to comply with the provisions of 37 CFR 3.81(b), the request cannot be granted at this time.


A review of Office database assignment records reflects that an assignment to Serono Genetics Institute, S.A. and Commissariat A L'Energie Atomique has been recorded. Therefore, upon submission of the required certificate of correction and fee, it would be appropriate for the Office to issue a certificate of correction to correct the front page of the Letters Patent to reflect that Serono Genetics Institute, S. A. and Commissariat A L'Energie Atomique were the assignees of record at the time of issuance of the application into a patent. *Note also 35 U.S.C. § 152.*

In view of the above and **after issuance of this application into a patent, the Certificates of Correction Branch is instructed to issue a certificate of correction upon submission by petitioner of a request for a certificate of correction (and fee) which sets forth Serono Genetics Institute, S.A. and Commissariat A L'Energie Atomique, as the assignees. No certificate of correction will be issued which sets forth an assignee other than the assignee set forth in this request. A copy of this decision must accompany the request for a Certificate of Correction.**

No further renewed request under 37 CFR 3.81(b) is necessary for consideration by the Office of Petitions for issuance of a certificate of correction in the name of the assignees set forth in this request, as this decision operates as an instruction to the Certificates of Correction Branch to issue the requested certificate of correction.

Alternatively, if petitioner desires to have the correct assignee data appear on the front page of the Letters Patent, petitioner may wish to consider filing a petition to withdraw the subject application from issue under 37 CFR 1.313(c)(2). The petition to withdraw from issue under 37 CFR 1.313(c)(2) must be accompanied by a request for continued examination (RCE) and submission (which may be a request under 37 CFR 3.81(b)).

Inquiries concerning this decision should be directed to the undersigned at (571) 272-3223. Any questions concerning issuance of a certificate of correction should be directed to the Certificates of Correction Branch at (703) 305-8309.


Marianne E. Jenkins
Petitions Examiner
Office of Petitions

MAR 8 2000

droplets on the surface. Alternatively, the film may comprise a matrix of hydrophillic areas surrounded by a hydrophobic region, the hydrophillic areas being sufficiently hydrophillic to allow adherence of individual liquid samples in the form of droplets on the hydrophillic areas. The film may be made of a material selected from the group consisting of polyimide, kapton, polycarbonate, PDMS and aluminum. The film may also have anisotropic thermal conductivity such that the thermal conductivity through a cross section of the film is greater than the thermal conductivity within a plane of the film. In yet another aspect of the device, the sample receiving regions may comprise a filament, wherein the filament is sufficiently hydrophillic to allow adherence of individual liquid sample volumes in the form of droplets on the filament. The filament may also be electrically conductive, and, in some embodiments, the liquid sample volumes may be heated by passing electric current through the filament. The sample transport member may be moved along the pathway by reels that frictionally engage the sample transport member.

BRIEF DESCRIPTION OF THE DRAWINGS

Figure 1 is a schematic view of one embodiment of the invention;

Figure 2 is a cross-sectional view of the substrate-thermal support assembly taken along II-II of Figure 1;

Figures 3A and 3B are cross-sectional views of embodiments of a microfluidic substrate according to the present invention;

Figure 4 is an exploded view of a microfluidic substrate according to the invention;

Figure 5 is an exploded view of the microfluidic substrate and the thermal support according to the invention;

Figure 6 is a cross-sectional view of another embodiment of a microfluidic substrate and thermal support system;

Figure 7 is a cross-sectional view of yet another embodiment of a microfluidic substrate and thermal support system according to the invention;

Figures 8-11 are cross-sectional views of the microfluidic substrate at various phases of assembly;

temperatures at which each of the steps is performed may be selected as appropriate for the primers and target sequences being used. For example, the steps for one method for performing PCR are as follows:

- denaturation of the DNA by heating the solution to 94°C, to completely separate the two strands of DNA and to remove the secondary structures;
- hybridization of the primer onto the single strand, achieved by lowering the temperature to allow specific pairing; and
- elongation of a strand of DNA by setting the temperature to the optimum for activity of the heat-stable polymerase, for example 72°C for certain enzymes.

After these three steps, which are herein defined as constituting a "cycle," denaturation is again carried out, and the newly synthesized DNA will be used as matrix. Cycles are repeated twenty to forty times, leading to an exponential increase in the amount of matrix. It will be appreciated that the number of cycles and the temperatures at which the various steps in the cycles are performed may be any value consistent with the desired amplification.

An example a protocol for amplification by PCR which has been carried in a microfluidic substrate according to the invention is provided in Example 1.

Temperature cycling and genetic analysis

In genetic analysis, numerous protocols exist which require temperature cycling. Amplification techniques which are derived from the PCR are known, such as RT-PCR, allele-specific PCR and Taq Man PCR (White, B.A., *Methods Mol Biol* 67:481-486 (1997); Delidow, B.C. *et al.*, *Methods Mol Biol* 58: 275-292 (1996), the contents of which are incorporated herein by reference in their entireties). Ligase chain reaction (LCR) techniques are also well known, including LCR, gap LCR, asymmetric gap LCR, reverse transcription LCR (RT-LCR), the oligonucleotide ligation assay (OLA) and PCR-OLA (Nikiforov, T., *Anal Biochem* 225: 201-209 (1995); Marshall, R.L., *PCR Methd Appl* 4: 80-84 (1994); Nickerson, D.A. *et al.*, *Proc Natl Acad Sci USA* 87: 8923-8927 (1990), the contents of which are incorporated herein by reference in their entireties). Cyclic sequencing reactions using clones or PCR reactions are known. Cyclic microsequencing (single nucleotide primer extension) reactions are known

reported fluorescence can be used to monitor the increase in reporter fluorescence. In one embodiment, a device such as the ABI Prism Sequence Detection System (PE Applied Biosystems) is used. In other embodiments, a detection device is integrated into the microfluidic device of the invention, or is integrated into a further microfluidic substrate operably linked to the microfluidic substrate of the invention. Example 6 below describes the use of devices of the present invention for genotyping using molecular beacons.

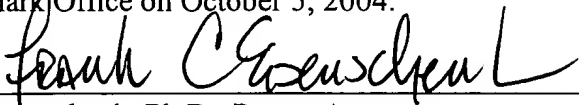
PCR- sequence-specific primers (SSP)

Genotyping may be carried out in accordance with the present invention using the method of sequence-specific primers (PCR-SSP) (Metcalf *et al.*, *Vox Sang* 77: 40-43 (1999), the contents of which is incorporated herein by reference in its entirety) also called allele-specific PCR (AS-PCR), a competitive multiplex PCR method using parallel reactions in which PCR amplification can be successfully performed only by using the primers whose 3' ends are an exact match to an allele. Sohda (*J. Clin. Lab Anal.* 13: 205-208 (1999), the contents of which is incorporated herein by reference in its entirety).

a. **Sample preparation for somatic cells genotyping : RT-PCR**

The present invention provides a device and processes for genotyping a sample using reverse-transcriptase and nested PCR of expressed sequences (RT-nested PCR), followed by cycle sequencing (Happ *et al.*, *Vet. Immunol. Immunopathol.* 69: 93-100 (1999), the contents of which is incorporated herein by reference in its entirety) which provides a degenerate PCR technique that can be used as a first step to identify and amplify the actual sequence when it is not completely known. Harwood *et al.* (*J. Clin. Microbiol.* 37: 3545-3555 (1999), the contents of which is incorporated herein by reference in its entirety). In one embodiment, amplification templates are produced by performing reverse-transcriptase PCR (RT-PCR) on total RNA. In one embodiment, the RT-PCR reaction is performed in a channel of the device, and reagents for subsequent reactions are added directly to the mixture in the device; alternately, RT-PCR may be performed outside the device, and an aliquot introduced into the device of the present invention.

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facsimile transmitted to the United States Patent
and Trademark Office on October 5, 2004.



Frank C. Eisenschenk, Ph.D., Patent Attorney

AMENDMENT UNDER 37 C.F.R. § 1.111
Examining Group 1637
Patent Application
Docket No. G-069US02CIP
Serial No. 09/772,280

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Examiner : Joyce Tung
Art Unit : 1637
Applicants : Yves Fouillet, Claude Vauchier, Jean-Frederic Clerc, Christine Peponnet,
Patricia Claustre, Raymond Charles, Nicolas Sarrut
Serial No. : 09/772,280
Filed : January 29, 2001
Conf. No. : 9257
For : Method for Carrying Out a Biochemical Protocol in Continuous Flow in a
Microreactor

Mail Stop Amendment
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313

AMENDMENT UNDER 37 C.F.R. § 1.111

Sir:

A Petition and Fee for a three-month Extension of Time through and including October 5, 2004, accompanies this Amendment.

In response to the Office Action dated April 5, 2004, please amend the above-identified patent application as follows:

In the Claims

Claims 1 – 8 (canceled)

9. (previously amended) A method for carrying out a chemical or biochemical protocol comprising:

depositing liquid sample volumes into a plurality of sample receiving regions on at least one mobile sample transport member; and

moving the sample transport member along a pathway such that said sample receiving regions move through at least one temperature regulated zone upon which a thermal transfer member acts, wherein said thermal transport member cycles between at least two temperatures while said sample receiving regions are moving through said at least one temperature regulated zone; and

wherein the protocol is carried out in an atmosphere sufficiently humid to reduce or prevent evaporation of the liquid sample volumes.

10. (original) The method of claim 9 further comprising adding at least one reagent to the sample receiving regions while the sample receiving regions are moving along said pathway.

11. (original) The method of claim 9 wherein the sample receiving regions comprise areas on a substrate.

12. (original) The method of claim 11 wherein the areas on the substrate comprise wells.

13. (original) The method of claim 12 wherein the sample receiving regions comprise a plate, having a plurality of wells therein, said wells having a thin film on their bottom surfaces.

14. (original) The method of claim 11 wherein the substrate is a film.

15. (original) The method of claim 14 wherein a surface of the film is sufficiently hydrophillic to allow adherence of individual liquid sample volumes in the form of droplets on the surface.

16. (original) The method of claim 14 wherein said film comprises a matrix of hydrophobic areas and hydrophillic areas, said hydrophillic areas being sufficiently hydrophillic to allow adherence of individual liquid samples in the form of droplets on said hydrophillic areas.

17. (original) The method of claim 11 wherein the substrate comprises a filament.

18. (original) The method of claim 17 wherein the filament is sufficiently hydrophillic to allow adherence of individual liquid sample volumes in the form of droplets on the filament.

19. (original) The method of claim 17 wherein the filament is conducting, and the droplets are heated by passing electric current through the filament.

20. (original) The method of claim 9 wherein said sample transport member moves along said pathway continuously.

21. (previously amended) The method of Claim 9 wherein said sample transport member moves along said pathway in steps.

22. (original) The method of claim 9 wherein said sample transport member is moved along said pathway by reels which frictionally engage the sample transport member.

23. (original) The method of claim 9 wherein the sample receiving regions are covered by a non-miscible liquid in order to prevent evaporation of the liquid sample volumes.

Claim 24 (canceled).

25. (original) The method of claim 9 wherein one of the at least two temperatures is about 50°C, and another of the at least two temperatures is about 94°C.

26. (original) The method of claim 9 wherein said thermal transfer member cycles through said at least two temperatures a plurality of times while said sample receiving regions are moving through said at least one temperature regulated zone.

27. (original) The method of claim 9 wherein said thermal transfer member cycles through said at least two temperatures from about 2 to about 35 times while said sample receiving regions are moving through said at least one temperature regulated zone.

28. (original) The method of claim 9 wherein the protocol is carried out in only one apparatus.

29. (original) The method of claim 9 wherein a plurality of sample receiving regions are processed in parallel in said at least one temperature regulated zone.

30. (original) The method of claim 9 wherein said chemical or biochemical protocol comprises a nucleic acid amplification procedure.

31. (original) The method of claim 30 wherein said chemical or biochemical protocol comprises a polymerase chain reaction.

32. (original) The method of claim 30 wherein said chemical or biochemical protocol comprises determining the identity of at least one polymorphic nucleotide in the product of said nucleic amplification procedure.

Claim 33-50 (canceled).

51. (previous presented) A method for carrying out a chemical or biochemical protocol comprising:

depositing liquid sample volumes into a plurality of sample receiving regions on at least one mobile sample transport member; and

moving the sample transport member along a pathway such that said sample receiving regions move through at least one temperature regulated zone upon which a thermal transfer member acts, wherein said thermal transport member cycles between at least two temperatures while said sample receiving regions are moving through said at least one temperature regulated zone;

wherein said sample transport member is moved along said pathway by reels which frictionally engage the sample transport member.

52. (previously presented) A method for carrying out a chemical or biochemical protocol comprising:

depositing liquid sample volumes into a plurality of sample receiving regions on at least one mobile sample transport member; and

moving the sample transport member along a pathway such that said sample receiving regions move through at least one temperature regulated zone upon which a thermal transfer member acts, wherein said thermal transport member cycles between at least two temperatures while said sample receiving regions are moving through said at least one temperature regulated zone; and

wherein the sample receiving regions are covered by a non-miscible liquid in order to prevent evaporation of the liquid sample volumes.

53. (previously presented) The method according to claim 9, wherein said pathway is a channel.

54. (previously presented) The method according to claim 9, wherein said thermal transfer member is a metal bar in fluid communication with a plurality of water sources that provide water having said at least two temperatures.

55. (previously presented) The method according to claim 9, wherein said sample transport member is continuously flowing through said at least one temperature regulated zone.

56. (previously presented) The method according to claim 11, wherein said substrate is a microfluidic substrate.

57. (previously presented) The method according to claim 56, wherein said microfluidic substrate comprises at least one microchannel.

58. (previously presented) The method according to claim 9, wherein said pathway is a microchannel.

59. (previously presented) The method according to claim 57, wherein said substrate is contacted with a thermal transfer member is a metal bar in fluid communication with a plurality of water sources that provide water having said at least two temperatures.

60. (previously presented) A method for carrying out a chemical or biochemical protocol comprising:

depositing liquid sample volumes into a plurality of sample receiving regions on at least one mobile sample transport member; and

moving the sample transport member along a pathway such that said sample receiving regions move through at least one temperature regulated zone upon which a thermal transfer member acts, wherein said thermal transport member cycles between at least two temperatures while said sample receiving regions are moving through said at least one temperature regulated zone.

61. (new) A chemical or biochemical protocol comprising the steps:

- a) providing at least one mobile sample transport member comprising at least one sample receiving region;
- b) applying a sample to said at least one sample receiving region;
- c) moving said at least one mobile transport member continuously along a pathway into a temperature regulated zone on which a thermal transfer member acts;
- d) cycling said thermal transfer member between at least two temperatures.

62. (new) The method of claim 61, wherein said thermal transfer member is cycled between at least two temperatures a plurality of times.

63. (new) The method of claim 61, wherein said at least one mobile transport member is continuously moved along a pathway into another temperature regulated zone on which another thermal transfer member acts.

64. (new) The method of claim 61, wherein said at least one mobile transport member is continuously moved along a pathway through a plurality of temperature regulated zones, each of said temperature regulated zones being acted upon by a thermal transfer member.

65. (new) The method of claim 61, further comprising the step of adding reagent to said sample in said sample receiving region.

66. (new) The method of claim 61, wherein said thermal transfer member is a metal bar in fluid communication with at least one heating, at least one cooling or at least one heating and at least one cooling reservoir containing a fluid.

67. (new) The method of claim 66, wherein said fluid is a gas.

68. (new) The method of claim 66, wherein said fluid is a liquid.

69. (new) The method of claim 68, wherein said liquid is water.

70. (new) The method of claim 62, wherein said thermal transfer member is a metal bar in fluid communication with at least one heating, at least one cooling or at least one heating and at least one cooling reservoir containing a fluid.

71. (new) The method of claim 70, wherein said fluid is a gas.

72. (new) The method of claim 70, wherein said fluid is a liquid.

73. (new) The method of claim 72, wherein said liquid is water.

74. (new) The method of claim 63, wherein said thermal transfer member is a metal bar in fluid communication with at least one heating, at least one cooling or at least one heating and at least one cooling reservoir containing a fluid.

75. (new) The method of claim 74, wherein said fluid is a gas.

76. (new) The method of claim 74, wherein said fluid is a liquid.

77. (new) The method of claim 76, wherein said liquid is water.

78. (new) The method of claim 64, wherein said thermal transfer member is a metal bar in fluid communication with at least one heating, at least one cooling or at least one heating and at least one cooling reservoir containing a fluid.

79. (new) The method of claim 78, wherein said fluid is a gas.

80. (new) The method of claim 78, wherein said fluid is a liquid.

81. (new) The method of claim 80, wherein said liquid is water.

Remarks

Claims 9-23, 25-32, and 51-60 are pending in the subject application and Applicants have added new claims 61-81. Support for the new claims can be found throughout the subject specification and in the claims as originally filed (for example, paragraphs 444-449 of the corresponding published U.S. Patent Application US-2001-0041357-A1). Entry and consideration of the amendments presented herein is respectfully requested. Accordingly, claims 9-23, 25-32, and 51-81 are currently before the Examiner. Favorable consideration of the pending claims is respectfully requested.

As an initial matter, Applicants gratefully acknowledge the Examiner's withdrawal of the previous rejection under 35 U.S.C. § 112. Applicants further wish to thank the Examiner for the courtesy of the interview of September 10, 2004. As discussed during the course of the interview, Applicants respectfully submit that the references singly or in combination fail to establish a *prima facie* case of obviousness for the claimed invention as "at least one temperature regulated zone upon which a thermal transfer member acts and wherein said thermal transfer member cycles between at least two temperatures" is not taught or suggested by the references. As discussed in the interview, a "temperature regulated zone" is at least a portion of the pathway, through which a sample moves, that is acted upon by a "thermal transfer member" that cycles between at least two temperatures. An exemplary temperature regulated zone is illustrated in Figure 1 of the subject application. In this example, a single temperature zone is schematically illustrated in one embodiment of a microfluidics device according to the invention in which a microfluidic substrate 100 is mounted upon a metal bar 900 which transfers heat to temperature regulated zone in the microfluidic substrate. As is illustrated by the Figure, the temperature regulated zone is a portion of the substrate upon which the thermal transfer member acts (*e.g.*, heating or cooling the substrate as required by a particular protocol). As further discussed during the interview, Figure 2 illustrates a device with three metal bars 900, 901, and 902 and the microfluidic substrate 100 of Figure 1. In Figure 2, each of the metal bars provides thermal regulation (*i.e.*, heating or cooling) to a separate temperature regulated zone of the microfluidic substrate; thus, there would be three distinct temperature regulated zones in the illustrated portion of the microfluidic substrate of Figure 2.

Claims 9-12, 21, 22, 25-32, 51, 55, and 60 are rejected under 35 U.S.C. § 103(a) as obvious over Bach *et al.* (U.S. Patent No. 6,413,780). Applicants respectfully traverse the rejection. As the Patent Office is aware, to establish the *prima facie* obviousness of a claimed invention all the claim limitations must be taught or suggested by the prior art (*In re Royka*, 490 F.2d 981, 180 U.S.P.Q. 580 (CCPA 1974)) and it is respectfully submitted that Bach *et al.* fail to teach or suggest all the limitations presented in the currently pending claims. The Office Action argues that Bach *et al.* teach, in Figure 3, a process path (11) that includes at least one temperature controller that keeps a portion of a first process path at a desired temperature and another temperature controller that keeps a second portion of the first process path at a second temperature. As discussed during the course of the interview, Applicants respectfully submit that Bach *et al.* fail to teach “temperature regulated zones” that cycle between at least two temperatures and upon which a thermal transfer member acts. As discussed above, a “temperature regulated zone” is a single section or region of a pathway that is acted upon by a thermal transfer member and which is cycled between at least two temperatures. This concept differs from the teachings of Bach *et al.* In the context of the subject invention, a single temperature regulated zone cycles between at least two different temperatures whereas the process path of Bach *et al.* is maintained at one temperature in a first temperature regulated zone (*i.e.*, a first portion of the process pathway) and a second temperature in a second temperature regulated zone (a second portion of the process pathway). Thus, Bach *et al.* fail to teach “temperature regulated zones” that are acted upon by separate and distinct thermal transfer members that cycle between at least two different temperatures. Additionally, it is respectfully submitted that Bach *et al.* fail to teach samples that are continuously moving through at least one temperature regulated zone that cycles between two different temperatures. Applicants respectfully submit that Bach *et al.* fail to teach each and every limitation of the independent claims of this application and, accordingly, reconsideration and withdrawal of the rejection is respectfully requested.

In addition, claims 13-20, 23, 52, 53, and 56-58 are rejected under 35 U.S.C. § 103(a) as obvious over Bach *et al.* (U.S. Patent No. 6,413,780) as applied to claims 9-12, 21, 22, 25-32, 51, 55, and 60 above, and further in view of Burns *et al.* (U.S. Patent No. 6,271,021). The Office Action states that one of ordinary skill in the art

“would have been motivated to modify the device of Bach *et al.* by applying the micro scale devices as taught by Burns *et al.* because Burns *et al.* teach that the sample receiving region on a plate substrate having a plurality of wells, the wells have a film which is hydrophilic and the device is in micro scale and the advantage is that each sample droplet is separated from each other so that the risk of contamination is reduced (See column 9, lines 6-8). In addition, the microdroplet transport avoids the current inefficiencies in liquid handling and mixing of reagents (See column 20, lines 16-17). (Office Action at page 6, last paragraph).

Applicants respectfully traverse.

As noted *supra*, Bach *et al.* fail to teach at least “one temperature regulated zone” that is acted upon by a thermal transfer member to cycle the temperature regulated zone between at least two different temperatures and Bach *et al.* also fail to teach samples that are continuously moving through at least one temperature regulated zone that is cycling between at least two different temperatures. Applicants further submit that the teachings of Burns *et al.* fail to remedy the defects noted with respect to the teachings of Bach *et al.* Burns *et al.* do not teach samples that are continuously moving through at least one temperature regulated zone that is cycling between at least two different temperatures. As indicated in column 8, lines 25-40 and illustrated in Figure 1, samples are moved to a thermally controlled reaction chamber (C) where mixing and reactions occur; the samples do not continuously move through the thermally controlled reaction chamber, rather they are held in the chamber. The reference further indicates that products arising in the reaction chamber (C) are then moved to an electrophoresis module (D) where migration data is gathered by a detector (E). Thus, the reference fails to teach that the samples continuously move through a temperature regulated zone that is acted upon by a thermal transfer member that cycles the zone between at least two temperatures.

The Office Action further argues that one skilled in the art “would have been motivated to modify the device of Bach *et al.* by applying the micro scale devices as taught by Burns *et al.* because Burns *et al.* teach that the sample receiving region on a plate substrate having a plurality of wells, the wells have a film which is hydrophilic and the device is in micro scale and the advantage is

that each sample droplet is separated from each other so that the risk of contamination is reduced. In addition, the microdroplet transport avoids the current inefficiencies in liquid handling and mixing of reagents". Applicants respectfully submit that one skilled in the art would not have been so motivated for the following reasons.

As the Patent Office is aware, the Court of Customs and Patent Appeals has held that a case of *prima facie* obviousness cannot be found where the suggested combination of references would require a substantial reconstruction and redesign of the elements shown in the primary reference as well as a change in the basic principle under which the primary reference was designed to operate. *In re Ratti*, 270 F.2d 810, 813, 123 U.S.P.Q. 349, 352 (CCPA 1959). In the case of the instant invention, the modification of the device of Bach *et al.* by applying the micro scale devices as taught by Burns *et al.* would require substantial reconstruction and redesign of the elements shown in the primary reference. For example, it would be necessary to completely redesign and construct a substantially different process path because the microfluidic substrate of Burns *et al.* would not appear to be an element that could be substituted for the containers that are loaded into the process path by the container loader and transporter taught by Bach *et al.* (see column 7, lines 42-46). Indeed, it would not appear that the liquid handling components of the Bach *et al.* device could be used to deliver reagents or samples into microfluidic substrate of Burns *et al.* Additionally, the device of Bach *et al.* lacks a means for energizing the silicon-based devices taught by Burns *et al.* and the device of Bach *et al.* would require substantial redesign and reconstruction to provide contact pads to which the heating elements of the microfluidic device of Burns *et al.* must be attached to accomplish the movement of the sample and its reaction in the reaction chamber (see Burns *et al.*, paragraph bridging columns 12-13). Accordingly, it is respectfully submitted that the combination of Bach *et al.* and Burns *et al.* fails to raise a *prima facie* case of obviousness and reconsideration and withdrawal of the rejection is respectfully requested.

Claims 54 and 59 are rejected under 35 U.S.C. § 103(a) as obvious over Bach *et al.* (U.S. Patent No. 6,413,780) as applied to claims 9-12, 20-22, 25, 26, 28, 30-32, 51, 53, and 60 above, and further in view of Leatti *et al.* (presumed by Applicants to be Leavitt *et al.*, U.S. Patent No. 5,002,870). The Office Action argues that one skilled in the art would have been motivated to use the temperature cyclers of Leavitt *et al.* in the method of Bach *et al.* in order to carry out biochemical

or chemical protocols because the temperature cyclers of Leavitt *et al.* is for a total of 30 cycles and is convenient and because the teachings of Leavitt *et al.* provide a metal bar in fluid communication. Applicants respectfully traverse.

To establish *prima facie* obviousness of a claimed invention, all the claim limitations must be taught or suggested by the prior art. *In re Royka*, 490 F.2d 981, 180 U.S.P.Q. 580 (CCPA 1974). In this regard, Applicants have reviewed the teachings of Leavitt *et al.* (column 17, lines 1-14) cited in the Office Action and have been unable to identify any mention of a metal bar in fluid communication with a plurality of water sources that provide water having said at least two temperatures. As is indicated in the paragraph 166 of the published application corresponding to this serial number,

“... the metal bar 900 is in communication with a system of valves (such as electrovalves or pressure valves) 910 through a system of pipes 920. The pipes 920 may be made of any conventional materials such as, for example, those used in traditional plumbing. The valves 910 may be actuated either manually or by an automated system controlled by a central processing unit. The valves 910 are, in turn, in communication with a plurality (three in the embodiment of FIG. 1) of reservoirs 930 by another set of pipes 940. The reservoirs 930 may be large tanks capable of holding a fluid. Each reservoir 930 is capable of maintaining the temperature of a fluid therein at a specified level by, for example, any of well-known heating or refrigeration means. The fluid in each reservoir 930 is maintained at a different temperature. In the present embodiment, the three reservoirs are maintained at 55°C, 72°C and 94°C. However, the number and temperatures of the reservoirs may be any combination consistent with the protocol to be performed. Thus, the fluid in the reservoirs may heat or cool the temperature regulated zones to any desired temperature. For example, in some embodiments, a reservoir at 37°C may be present in addition to the reservoirs at 55°C, 72°C and 94°C. It will be appreciated that in embodiments employing more than one temperature regulated zone, each of the reservoirs may be in fluid communication with all of the temperature regulated zones or only with a portion of the temperature regulated zones in accordance with the protocol to be performed.”

Thus, it is respectfully submitted that the combination of Bach *et al.* and Leavitt *et al.* fail to teach each and every limitation of the claimed invention and, accordingly, reconsideration and withdrawal of the rejection under 35 U.S.C. § 103(a) is respectfully requested.

It should be understood that the amendments presented herein have been made solely to expedite prosecution of the subject application to completion and should not be construed as an indication of Applicants' agreement with or acquiescence in the Examiner's position. Applicants expressly reserve the right to pursue the invention(s) disclosed in the subject application, including any subject matter canceled or not pursued during prosecution of the subject application, in a related application.

In view of the foregoing remarks and amendments to the claims, Applicants believe that the currently pending claims are in condition for allowance, and such action is respectfully requested.

The Commissioner is hereby authorized to charge any fees under 37 C.F.R. §§1.16 or 1.17 as required by this paper to Deposit Account No. 19-0065.

Applicants invite the Examiner to call the undersigned if clarification is needed on any of this response, or if the Examiner believes a telephonic interview would expedite the prosecution of the subject application to completion.

Respectfully submitted,



Frank C. Eisenschenk, Ph.D.

Patent Attorney

Registration No. 45,332

Phone No.: 352-375-8100

Fax No.: 352-372-5800

Address: P.O. Box 142950
Gainesville, FL 32614-2950

FCE/sl

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UNITED STATES PATENT AND TRADEMARK OFFICE

CERTIFICATE OF CORRECTION

PATENT NO. : 6,977,145

Page 1 of 2

APPLICATION NO.: 09/772,280

DATED : December 20, 2005

INVENTORS : Yves Fouillet, Claude Vauchier, Jean-Frederic Clerc, Christine Peponnet,
Patricia Claustre, Raymond Charles, and Nicolas Sarrut

It is certified that errors appear in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

Title page,

No. (75) "Serono Genetics Institute S.A." should read

--Serono Genetics Institute S.A. and Commissariat a l'Energie Atomique--.

Column 7,

Line 62, "along I-II" should read --along II-II--.

Column 25,

Line 25, "Eallele-specific" should read --allele-specific--.

Column 42,

Line 6, "Genotypin:" should read --Genotyping:--.

Column 62,

Line 27, "whwrein" should read --wherein--.

Column 63,

Line 34, "such hat" should read --such that--.

Column 64,

Line 8, "member is" should read --member that is--.

MAILING ADDRESS OF SENDER:

Saliwanchik, Lloyd & Saliwanchik

P.O. Box 142950

Gainesville, FL 32614-2950

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It is certified that errors appear in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

Column 65,

Line 1, "method claim 47" should read --method of claim 47--.

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Saliwanchik, Lloyd & Saliwanchik

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Gainesville, FL 32614-2950

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Saliwanchik, Lloyd & Saliwanchik
P.O. Box 142950
Gainesville, FL 32614-2950

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PTAS
KNOBBE, MARTENS, OLSON & BEAR, LLP
DANIEL HART
620 NEWPORT CENTER DRIVE
SIXTEENTH FLOOR
NEWPORT BEACH, CA 92660



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ASSIGNOR:

FOUILLET, YVES

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ASSIGNOR:

VAUCHIER, CLAUDE

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ASSIGNOR:

CLERC, JEAN-FREDERIC

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ASSIGNOR:

PEPONNET, CHRISTINE

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ASSIGNOR:

CLAUSTRE, PATRICIA

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ASSIGNOR:

CHARLES, RAYMOND

DOC DATE: 05/23/2001

ASSIGNOR:

SARRUT, NICOLAS

DOC DATE: 05/23/2001

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Attorney Responsible
Initial _____

ASSIGNEE:

GENSET, S.A.
24, RUE ROYALE
75008 PARIS, FRANCE

ASSIGNEE:

COMMISSARIAT A L'ENERGIE ATOMIQUE
31-33 RUE DE LA FEDERATION
75752 PARIS CEDEX 15, FRANCE

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MAURICE CARTER, EXAMINER
ASSIGNMENT DIVISION
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